REMARKS

Claims 1, 6-7, 9-13, 18, 20-21, 23-26 and 35-36 are pending after entry of this paper. Claims 1, 6-7, 9-13, 18, 20-21, 23-26 and 35-36 have been rejected. Claims 2-5, 8, 14-17, 19, 22 and 27-34 have been cancelled without prejudice. Applicants reserve the right to pursue cancelled claims in a continuing application.

Claim 1 has been amended to incorporate the subject matter of claim 8. Specifically, the subject matter of claim 8 is now presented in step (iii) of claim 1. Support may be found in the previously presented claim 8.

Claim 1 has been further amended to replace the phrase "infecting a virus mixed solution of the homologous recombination" with the phrase "cotransfecting said fragment within the ribonucleotide reductase gene locus with a viral DNA in..." Support for these amendments may be found on pages 36-40 (Virus Preparation).

Claim 1, 6 and 35 has been amended to replace the phrase "transcriptional initiation regulatory region of a human calponin gene" with the phrase "region containing a promoter of the human calponin gene." Support for these amendments may be found throughout the instant specification, for example at pages 36-40 (Virus Preparation) and at the paragraph bridging pages 22 and 23. Claim 6 has been further amended to depend only from claim 1.

Claim 9 has been amended to depend from claim 1 instead of the presently cancelled claim 8, since the subject matter of claim 8 is now incorporated into claim 1.

Claim 20 has been amended to replace the term "protein" with the term "peptide."

Claim 21 has been amended to incorporate the subject matter of the presently cancelled claim 22.

Claim 35 has been amended to clarify steps in producing a cell-specific HSV vector as outlined in Example A-5.

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Withdrawn Rejections

Applicants acknowledge the withdrawal of all rejections to claims 5 and 19 due to cancellation of claims 5 and 19. Applicants further acknowledge the withdrawal of rejections to claim 10-13 under 35 U.S.C. §112, second paragraph as being indefinite; to claims 29-36 under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps; to claims 1, 3-18, 20-22, and 25-28 under 35 U.S.C. §103(a) as being unpatentable over Van Meir, et al. (PGPUB 2005/0074430) in view of LaFace (U.S. Patent No. 6,649,158) and Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001); and to claims 26-34 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement.

Claim Objections

Claims 29 is objected to for reciting "promote apoptosis;" whereas it should recite "promotes apoptosis." However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claim 29 rendering the objection to this claim moot.

Claim 27 is objected to under 37 CFR 1.75(c) as being of improper dependent form. However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claim 27 rendering the objection to this claim moot.

Response to Rejections under 35 U.S.C. §112, first paragraph – Enablement

Applicants acknowledge the withdrawal of the rejections of claims 5 and 26-34 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement

Claims 1, 3, 4, 6-13, 18, and 20-34 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Examiner contends that the specification, while being enabling for an HSV vector comprising SEQ ID NO: 3 operably linked to an ICP4 gene and a TK gene, allegedly does not provide enablement for any other vector comprising SEQ ID NO: 1 or SEQ ID NO: 2 (Office Action – page 6). Applicants respectfully disagree.

As an initial matter, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to recite "a region containing a promoter of the human calponin gene comprising the nucleotide sequence shown in SEQ ID NO: 1." Support for this amendment may be found throughout the instant specification and claims, for example at page 23, lines 1-7 of the specification as originally filed.

The Examiner contends that "[a]lthough Yamamura et al. teach that the sequence between positions -260 and -219 is essential for inducing calponin gene transcription in HOS (osteosarcoma) and HMC (mesangial) cell lines, they do not teach that this region can by itself promote tissue specificity" (Office Action – page 7). Applicants assert that the presently

amended claim 1 is directed to a region containing a promoter of the human calponin gene comprising the nucleotide sequence shown in SEQ ID NO: 1. Thus, it is irrelevant based on the limitations of claim 1 that Yamamura does not teach that the sequence between positions -260 and -219 (SEQ ID NO: 1) can by itself promote tissue specificity.

Furthermore, the Examiner contends that "[t]here is a difference between induction of transcription and tissue/cell specificity. Absent evidence to the contrary, the sequence between positions -260 and -219 can perform equally well in different tissues/cells (*i.e.*, does not confer cell specificity) and it is possible that additional regions of the calponin promoter, other than positions -260 and -219, are required to confer tissue/cell specificity" (Office Action – pages 7-8). Applicants assert that presently amended claim 1 affords the presence of additional regions of the calponin promoter other than SEQ ID NO: 1, because claim 1 has been amended to recite "a region containing a promoter of the human calponin gene comprising the nucleotide sequence shown in SEQ ID NO: 1," while explicitly defining the limitation "wherein the HSV vector is not expressed or replicated in normal differentiated cells" (emphasis added). Therefore, one skilled in the art would readily understand that the induction of transcription and tissue/cell specificity are not different when the gene is expressed selectively in particular cell. The specification as originally filed at the paragraph bridging pages 8 and 9 discloses the following:

> Meanwhile, the present inventors have found that a calponin gene, which is thought to be a differentiation marker of smooth muscles, is expressed in the tumor cells of human-derived sarcoma, and reported this fact for the first time (*Int. J. Cancer* 79, 245-250, 1998; *Sarcoma* 3, 107-113, 1999; *Intern. J. Cancer* 82, 678-686, 1999). Thereafter, there have been continuous domestic and foreign reports that calponin genes express abnormally in almost 20 types of human malignant tumor derived from mesenchymal cells such as bone sarcoma and soft tissue sarcoma as well as in gastrointestinal stromal tumor (GIST) and salivary gland sarcoma,

> fibrosarcoma, malignant neurinoma. ..... In an adult body, the calponin gene selectively expresses in the smooth muscle cell and is regarded as a differentiation marker of the vessels and gastrointestinal tract (*Physiol. Rev.* 75, 487-517, 1995).

Assuming *arguendo* that "the art and the specification only teach SEQ ID NO: 3 (i.e., the full length promoter) as having tissue specificity ... [and] one of skill in the art would readily understand that other regions other than of the positions -260 and -219 are important for promoting cell specific activity" according to the Examiner (Office Action – page 8), claim 1 has been amended to recite "a region containing a promoter of the human calponin gene comprising the nucleotide sequence shown in SEQ ID NO: 1." The Examiner's contention is misplaced, because even if regions other than SEQ ID NO: 1 of the calponin promoter are essential for promoting a cell specific activity, "regions other than SEQ ID NO: 1 in the calponin promoter" are also included in "a region containing a promoter of the human calponin gene comprising the nucleotide sequence shown in SEQ ID NO: 1".

Therefore, contrary to the Examiner's contention, one skilled in the art could make and use the claimed invention without undue experimentation. Accordingly, reconsideration and withdrawal of the enablement rejection of claims 1, 3, 4, 6-13, 18, and 20-34 under 35 U.S.C. §112, first paragraph are respectfully requested.

Claims 1, 3, 4, 6-13, 18, and 20-36 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Examiner contends that the claims as presented allegedly do not require the calponin promoter to drive the expression of the transcription factor essential for HSV replication. According to the Examiner, the claims as presented require the transcription factor to be expressed from the ICP4 gene promoter, which

although enabling, would confer cell specificity, a property essential for the claimed invention (Office Action – pages 19-20). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to replace the phrase "the transcriptional initiation regulatory region of an ICP4 gene" with the phrase "the region containing a promoter of the human calponin gene." Support for this amendment may be found throughout the instant specification and claims, for example claim 1 as originally filed. Applicants assert that one skilled in the art while reading the presently amended claims would readily recognize that the calponin promoter regulates the transcription of the gene encoding a transcription factor essential for HSV replication and thymidine kinase, and therefore would be cell specific as required by the claimed invention.

With respect to claims 35 and 36, the Examiner alleges that neither the art nor the specification teaches that a solution comprising a cell can be inserted into a gene fragment. In order to expedite prosecution and solely for the purpose of allowance of the instant application, applicants have amended claim 35 to clarify the steps for producing the claimed HSV vector. Specifically, the steps now recite the subject matter as outlined in Example A-5 "Virus Preparation."

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph enablement rejection of claims 1, 3, 4, 6-7, 9-13, 18, and 20-36.

Response to Rejections under 35 U.S.C. §112, first paragraph – Written Description

Claims 1, 3, 4, 6-13, 18, and 20-34 stand rejected under 35 U.S.C. §112, first paragraph for lack of written description. Specifically, the Examiner contends that the specification does not provide support for the phrase "normal differentiated cells," while only allegedly supporting the phrase "normal adult cells." Accordingly, the Examiner contends that such recitation adds new matter (Office Action – page 16). Applicants respectfully disagree.

On the contrary, even though the specification does not explicitly recite "normal differentiated cells," MPEP 2163 states that "[t]o comply with the written description requirement of 35 U.S.C. 112, para. 1, [sic] each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure" (emphasis added). Applicants assert that it would be inherent that the claimed invention selectively avoids normal differentiated cells, since the specification provides an ample number of examples where only proliferating cells are specifically targeted (See for Example, page 27, lines 23-24; page 3, lines 12-17 of the instant specification). In the art, the proliferating cells are defined as cells that "grow or produce by multiplication of parts or cell division" (*Random House Unabridged Dictionary*, Random House, Inc., New York 2006); whereas, normal differentiated cells do not proliferate. Therefore, it would be inherent to one skilled in the art that the specification provides enough support for the claimed HSV vector that does not express or replicate in normal differentiated cells.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejection of claims 1, 3, 4, 6-13, 18, and 20-34 in view of the above arguments.

Claims 1, 3, 4, 6-13, 18, and 20-36 stand rejected under 35 U.S.C. §112, first paragraph for lack of written description. Specifically, the Examiner contends that the specification does not provide support for the phrase "under the control of said transcriptional initiation regulatory region of the ICP4 gene" as recited in the previously amended claims 8 and 9 and therefore adds new matter (Office Action – page 17). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have incorporated the subject matter of the presently cancelled claim 8 into claim 1. Claim 1 has been further amended to clarify that "a DNA that encodes a desired protein linked downstream of the ICP4 gene, and expresses the desired protein under the control of said region containing a promoter of the human calponin gene" as noted by the Examiner (Office Action – page 18). Support for this amendment may be found throughout the instant specification and claims, for example, see paragraph 1 on page 26.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 1, 3, 4, 6-13, 18, and 20-36.

Response to Rejections under 35 U.S.C. §112, second paragraph

Applicants acknowledge the withdrawal of rejections to claims claim 10-13 under 35 U.S.C. §112, second paragraph as being indefinite; and to claims 29-36 under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps.

Claim 21 has been rejected under 35 U.S.C. §112, second paragraph for being incomplete. Specifically, the Examiner alleges that the above-referenced claim is missing steps

disclosing how the suppression of viral expression/replication is achieved (Office Action – page 5). Applicants respectfully disagree with this assertion.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 21 in order to clarify the step of suppressing the viral expression/replication by incorporating the subject matter of presently cancelled claim 22 to recite in step (iii) "suppressing the expression/replication of the vector at a later desired period by administering an antiviral drug, wherein said antiviral drug is aciclovir or ganciclovir."

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection of claim 21.

Claims 29 and 30 have been rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that it is not clear based on the disclosure of claim 29, how inhibition of myofibroblast proliferation and expression of a pro-apoptotic factor in myofibroblasts leads to inhibition of apoptosis in malignant tumors (Office Action – pages 5-6). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claims 29 and 30 without prejudice. Therefore, the rejection of claims 29 and 30 under 35 U.S.C. §112, second paragraph is now moot.

Claims 29-34 have been rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that the term "the gene, protein or peptide" has insufficient antecedent basis (Office Action – page 14). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claims 29-34 rendering this rejection moot. Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 29-34.

Claims 35 and 36 have been rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that the scope of the claim is difficult to ascertain. (Office Action – page 13). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 35 to clarify that a DNA fragment in step (a) contains a region containing a promoter of the human calponin gene, the ICP4 gene encoding a transcription factor essential for initiation of a herpes viral replication which is integrated downstream of the region containing said promoter; a DNA that encodes a desired protein linked downstream of the ICP4 gene, and expresses the desired protein under the control of said region containing a promoter of the human calponin gene, and a thymidine kinase gene. This DNA fragment is then inserted into the ribonucleotide reductase gene locus by homologous recombination (step (b)) and cotransfected within the ribonucleotide reductase locus

with a viral DNA in a cell that activates the region containing a promoter of the human calponin gene or a cell that expresses the human calponin gene (step (c)). Finally, a single clone is purified by limiting dilution without using agarose overlay assay where the expression of a gene integrated in the HSV vector is an index, where the HSV vector is not expressed or replicated in normal differentiated cells and that is capable of suppressing its replication at a desired period by using the thymidine kinase gene (step (d)). Applicants assert that the scope of the presently amended claim 35 is clear and would be understood by one skilled in the art.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 35 and 36.

Claims 6 and 7 have been rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that since the art does not teach more than one human calponin gene, it is not clear what applicants mean by the recitation of "a human calponin gene." (Office Action – page 14). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 6 to replace the phrase "a human calponin gene" with the the phrase "the human calponin gene." Applicants have further amended claims 1 and 35 thus clearly referring to the human calponin gene recited in the art.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 6 and 7.

Claims 1, 3, 4, 6-13, 18, and 20-34 have been rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that it is not clear what applicants mean by "infecting a virus mixed solution of the homologous recombination to a cell" as recited in claim 1. The Examiner, further, contends that allegedly the term "a ribonucleotide reductase locus" is not clear (Office Action – pages 14-15). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 for clarification. Specifically, a DNA construct, *i.e.*, a DNA fragment comprising the region containing promoter of the human calponin gene inserted into the ribonucleotide reductase gene losus by a homologous recombination, of step (i) is cotransfected with a viral DNA in "a cell that activates the transcription initiation regulatory region of the human calponin gene or a cell that expresses the human calponin gene." Support for this amendment may be found on page 43 (Example B-1) of the instant application. Furthermore, applicants have amended claim 1 to replace the term "a ribonucleotide reductase locus" with the term "the ribonucleotide reductase locus," thus clearly referring to the ribonucleotide reductase locus recited in the art as suggested by the Examiner.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 1, 2, 4, 6-13, 18, and 20-34.

Claims 31-34 have been rejected under 35 U.S.C. §112, second paragraph as being incomplete for omitting allegedly essential elements which result in a gap between the elements (Office Action – page 15). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claims 31-34 rendering this rejection moot. Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 31-34.

Response to Rejections under 35 U.S.C. §103(a) over Martuza, et al. in view of Yamamura, et al., and Chung, et al.

Claims 1, 3, 6 and 7 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al., (U.S. Patent No. 5,728,379, of record) in view of Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001) and further in view of Chung, et al., (*J. Virol*, 73:7556-7564, 1999). According to the Examiner, Martuza, et al., allegedly teach an HSV vector with a cell-specific promoter that drives the expression of ICP4, an essential HSV gene, and the intact TK (thymidine kinase) gene. However, Martuza, et al., do not teach the calponin promoter of the 4F2 enhancer, but allegedly would be obvious in view of Yamamura, et al., disclosure (Office Action – page 7). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to incorporate the subject matter of claim 8, which contains presumably allowable subject matter because it has not been rejected for obviousness over Martuza in view of Yamamura and Chung. Specifically, claim 1

has been amended to recite step (iii) "a DNA that encodes a desired protein linked downstream of the ICP4 gene, and expresses the desired protein under the control of said region containing a promoter of the human calponin gene." Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Martuza, et al. in view of Yamamura, et al. and Chung, et al. are respectfully requested.

Response to Rejections under 35 U.S.C. §103(a) over Chung, et al. in view of Yamamura, et al.

Claims 1, 3, 4, 6, 7, 14, 16-18, 20, and 25-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chung, et al., (*J. Virol*, 73:7556-7564, 1999) in view of Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001). The Examiner alleges that the combined teachings of Chung, et al., and Yamamura, et al., disclose an HSV vector that uses two promoters comprising the calponin promoter driving the expression of the γ34.5, wherein the ICP4 gene is intact (Office Action – page 11). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to incorporate the subject matter of claim 8, which contains presumably allowable subject matter because it has not been rejected for obviousness over Chung in view of Yamamura. Specifically, claim 1 has been amended to recite step (iii) "a DNA that encodes a desired protein linked downstream of the ICP4 gene, and expresses the desired protein under the control of said region containing a promoter of the human calponin gene." Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Chung, et al. in view of Yamamura, et al. are respectfully requested.

Response to Rejections under 35 U.S.C. §103(a) over Chung, et al. in view of Yamamura, et al. and Tjuvajev, et al.

Claims 1, 3, 4, 6, 7, 14, 16-18, 20, and 23-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chung, et al., (*J. Virol*, 73:7556-7564, 1999) in view of Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001) and further in view of Tjuvajev, et al. (Cancer Research, 58:4333-4341, 1998). According to the Examiner, the combined teachings of Chung, et al., and Yamamura, et al. as applied to claims 3-7, 14, 16-20 and 25-28 do not teach detecting the *in vivo* distribution of the vector by determining Thymidine Kinase activity using positron emission tomography (PET) and FIAU labeled with ^{124}I, which allegedly taught by Tjuvajev, et al. (Office Action – page 12). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to incorporate the subject matter of claim 8, which contains presumably acceptable subject matter because it has not been rejected for obviousness over Chung in view of Yamamura and Tjuvajev. Specifically, claim 1 has been amended to recite step (iii) "a DNA that encodes a desired protein linked downstream of the ICP4 gene, and expresses the desired protein under the control of said region containing a promoter of the human calponin gene." Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Chung, et al. in view of Yamamura, et al. and Tjuvajev, et al. are respectfully requested.

Response to Rejections under 35 U.S.C. §103(a) over Chung, et al. in view of Yamamura, et al. Van Meir, et al. and Miyatake, et al.

Claims 1, 3, 4, 6, 7, 18, 20-22 and 25-34 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chung, et al., (*J. Virol*, 73:7556-7564, 1999) in view of Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001) and further in view of Van Meir, et al, (PGPUB 2005/0074430) and Miyatake, et al., (*Stroke*, 30:2431-2439, 1999). According to the Examiner, Chung, et al. teach an HSV vector comprising the cell cycle regulated B-myb promoter integrated upstream of the predetermined viral gene γ34.5 and an intact thymidine kinase gene, wherein B-myb promoter-γ34.5 sequence is inserted in the ribonucleotide reductase locus. Whereas, Yamamura, et al., allegedly teach a replication competent HSV vector comprising the calponin promoter as set forth in SEQ ID NO. 3, the 4F2 enhancer upstream of the promoter, and Van Meir, et al. allegedly teach using ganciclovir to terminate the propagation of the HSV vector. Finally, Miyatake, et al. allegedly teach HSV vectors that inhibit smooth muscle cell proliferation (Office Action – pages 21-24). According to the Examiner, this combination of prior art makes the claimed invention obvious. Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to incorporate the subject matter of claim 8, which contains presumably allowable subject matter because it has not been rejected for obviousness over Chung in view of Yamamura, Van Meir and Miyatake. Specifically, claim 1 has been amended to recite step (iii) "a DNA that encodes a desired protein linked downstream of the ICP4 gene, and expresses the desired protein under the control of said region containing a promoter of the human calponin gene." Accordingly, reconsideration and

withdrawal of the rejection under 35 U.S.C. §103(a) over Chung, et al. in view of Yamamura, et al., Van Meir, et al, and Miyatake, et al. are respectfully requested.

Response to Provisional Non-Statutory Double Patenting Rejection

Applicants acknowledge the withdrawal of the rejection of claim 5 on the ground of non-statutory double patenting.

Claims 1, 3, 4, 6 and 7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/477,797 (Publn. No. 2004-0197308) in view of Martuza (U.S. Patent No. 5,728,379, of record) and Yamamura (*Cancer Research*, 61:3969-3977, 2001; of record). Since the conflicting claims have not in fact been patented, this is a provisional obviousness-type double patenting rejection. The Examiner maintains that the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

In response , applicants submit that the amendments to claim 1, *i.e.*, incorporation of subject matter of claim 8, which contains presumably allowable subject matter because it has not been rejected for obviousness, obviate the provisional obviousness-type double patenting rejection.

Withdrawal of the rejection is respectfully requested.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent

claims 1 and 35 from which all of the dependent claims 6, 7, 9-13, 18, 20-21, 23-26, and 36 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4022.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4022.

Respectfully submitted,
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